

PATENT
Serial No. 10/750,934
Docket No. 0101.00

Claims:

The following listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently Amended) A pharmaceutical formulation for pulmonary administration as a powder, the pharmaceutical formulation comprising:
particulates ~~comprising~~ consisting essentially of an active agent particle ~~particles~~
in a phospholipid lipid matrix, ~~the active agent having a solubility in water of less than~~
~~1.0 mg/ml; wherein the active agent particles are dispersed throughout the phospholipid~~
~~matrix; and~~
wherein at least 90% of the active agent particles ~~in the pharmaceutical~~
~~formulation~~ have a geometric diameter less than $3\ \mu\text{m}$ and wherein the particulates
have a mass median diameter less than $10\text{--}20\ \mu\text{m}$ and a bulk density of less than about
 $0.5\ \text{g/cm}^3$.
2. (Currently Amended) A pharmaceutical formulation according to claim 1 wherein
the particulates have a mass median aerodynamic diameter less than ~~$10\ \mu\text{m}$~~ about $2.6\ \mu\text{m}$.
3. (Currently Amended) A pharmaceutical formulation according to claim 1 wherein
~~the particulates have a mass median diameter less than $5\ \mu\text{m}$~~ a formulation emitted
dose is at least about 93 percent.
4. (Currently Amended) A pharmaceutical formulation according to claim 1 wherein
~~at least 95% of the active agent particles have a geometric diameter less than $3\ \mu\text{m}$~~ a
formulation fine particle fraction of less than $3.3\ \mu\text{m}$ is at least about 72 percent.

PATENT
Serial No. 10/750,934
Docket No. 0101.00

5. (Currently Amended) A pharmaceutical formulation according to claim 1 wherein ~~at least 50% of the active agent particles have a geometric diameter between 0.5 μ m and 3 μ m~~ the formulation exhibits an Ostwald ripening as depicted in Fig 1.
6. (Currently Amended) A pharmaceutical formulation according to claim 1 wherein ~~at least 50% of the active agent particles have a geometric diameter between 1 μ m and 3 μ m~~ the formulation provides for the delivery to the lung of a dose of at least about 5 mg in a single inhalation.
7. (Original) A pharmaceutical formulation according to claim 1 wherein the lipid matrix comprises one or more phospholipids.
8. (Currently Amended) A pharmaceutical formulation according to claim 1 wherein the lipid matrix comprises one or more of dipalmitoylphosphatidylcholine, ~~distearylphosphatidylcholine~~ distearylphosphatidylcholine, diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated phosphatidylinositols.
9. (Original) A pharmaceutical formulation according to claim 1 wherein the particulates are hollow.
10. (Original) A pharmaceutical formulation according to claim 1 wherein the particulates are porous.
11. (Original) A pharmaceutical formulation according to claim 1 wherein the particulates are hollow and porous.

PATENT
Serial No. 10/750,934
Docket No. 0101.00

12. (Currently Amended) A pharmaceutical formulation according to claim 1 wherein ~~the pharmaceutical formulation has a bulk density of less than 0.5 g/cm³~~ the active agent comprises tobramycin.
13. (Original) A pharmaceutical formulation according to claim 1 wherein the pharmaceutical formulation has a bulk density of less than 0.3 g/cm³.
14. (Original) A pharmaceutical formulation according to claim 1 wherein the pharmaceutical formulation has a bulk density of less than 0.2 g/cm³.
15. (Original) A pharmaceutical formulation according to claim 1 wherein the particulates are in dry powder form for aerosolization in a dry powder inhaler.
16. (Original) A pharmaceutical formulation according to claim 1 wherein the particulates are suspended in a propellant for aerosolization in a metered dose inhaler.
17. (Original) A pharmaceutical formulation according to claim 1 wherein the particulates are suspended within a liquid for aerosolization in a nebulizer.
18. (Original) A pharmaceutical formulation according to claim 1 wherein the active agent particle is crystalline.
19. (Original) A pharmaceutical formulation according to claim 1 wherein the particulate further comprises a polyvalent cation.
20. (Currently Amended) A pharmaceutical formulation according to claim 1 wherein the active agent has a solubility in water of less than ~~[[0.1]]~~ 1.0 mg/ml.
21. (Currently Amended). A pharmaceutical formulation according to claim 1 wherein the particulates are formed by spray drying with a blowing agent.

PATENT
Serial No. 10/750,934
Docket No. 0101.00

22. (Original) A pharmaceutical formulation according to claim 1 wherein the insoluble active agent comprises an antimycotic agent.
23. (Withdrawn) A method of making a pharmaceutical formulation for pulmonary administration, the method comprising: suspending active agent particles and a hydrophobic material in a liquid feedstock, wherein at least 90% of the active agent particles have a geometric diameter less than 3 μm ; and spray drying the feedstock suspension to produce particulates comprising an active agent particle at least partially in the hydrophobic material.
24. (Withdrawn) A method according to claim 23 wherein the feedstock comprises water and wherein the active agent has a solubility in water of less than 1.0 mg/ml.
25. (Withdrawn) A method according to claim 23 further comprising collecting the particulates.
26. (Withdrawn) A method according to claim 25 wherein the collected particulates have a mass median diameter less than 20 μm .
27. (Withdrawn) A method according to claim 25 wherein the collected particulates have a mass median diameter less than 10 μm .
28. (Withdrawn) A method according to claim 23 wherein 95% of the active agent particles have a geometric diameter less than 3 μm .
29. (Withdrawn) A method according to claim 23 wherein the hydrophobic material comprises a lipid.
30. (Withdrawn) A method according to claim 23 wherein the hydrophobic material comprises a phospholipid.

PATENT
Serial No. 10/750,934
Docket No. 0101.00

31. (Withdrawn) A method according to claim 23 wherein the hydrophobic material comprises a hydrophobic amino acid.
32. (Withdrawn) A method according to claim 23 further comprising adding an emulsifying agent to the feedstock.
33. (Withdrawn) A method according to claim 23 wherein the emulsifying agent comprises distearoyl phosphatidylcholine.
34. (Withdrawn) A method according to claim 23 further comprising adding a blowing agent to the feedstock.
35. (Withdrawn) A method according to claim 23 further comprising adding a polyvalent cation to the feedstock.
36. (Withdrawn) A method according to claim 23 wherein the feedstock is spray dried in a manner to produce particulates having a bulk density of less than 0.5 g/cm^3 .
37. (Withdrawn) A pharmaceutical formulation prepared by a method according to claim 23.
38. (Currently Amended) A pharmaceutical formulation for pulmonary administration, the pharmaceutical formulation comprising:
particulates comprising an consisting essentially of active agent amphotericin-B particle particles in a lipid matrix comprising a phospholipid, the active agent having a solubility in water of less than 1.0 mg/ml and wherein the active agent particles are dispersed throughout the phospholipid matrix; and
wherein at least 90% of the amphotericin-B active agent particles in the pharmaceutical formulation have a geometric diameter less than $3 \mu\text{m}$ and wherein the particulates are hollow and/or porous, and have a mass median diameter less than $20 \mu\text{m}$, a bulk density of less than about 0.5 g/cm^3 and a mass median aerodynamic

PATENT
Serial No. 10/750,934
Docket No. 0101.00

diameter less than about 2.6 μm .

39. (Currently Amended) A pharmaceutical formulation according to claim 38 wherein ~~the particulates have a mass median diameter less than 10 μm~~ the formulation provides for the delivery to the lung of a dose of at least about 5 mg in a single inhalation.

40. (Original) A pharmaceutical formulation according to claim 38 wherein the particulates have a mass median diameter less than 5 μm .

41. (Currently Amended) A pharmaceutical formulation according to claim 38 wherein ~~at least some of the particulates comprise a plurality of amphotericin B particles in a lipid matrix~~ a formulation fine particle fraction of less than 3.3 μm is at least about 72 percent.

42. (Currently Amended) A pharmaceutical formulation according to claim 38 wherein ~~the amphotericin B particles are crystalline~~ the formulation provides for the delivery to the lung of a dose of at least about 5 mg in a single inhalation.

43. (Cancelled).

44. (Currently Amended) A pharmaceutical formulation according to claim 38 wherein the ~~lipid matrix~~ comprises one or more of dipalmitoylphosphatidylcholine, distearylphosphatidylcholine distearoylphosphatidylcholine, diarachidoylphosphatidylcholine dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated phosphatidylinositols.

45-46 (Cancelled)

PATENT
Serial No. 10/750,934
Docket No. 0101.00

47. (Original) A pharmaceutical formulation according to claim 38 wherein the particulates have a bulk density less than 0.3 g/cm^3 .
48. (Original) A pharmaceutical formulation according to claim 38 wherein the particulates have a bulk density less than 0.2 g/cm^3 .
49. (Original) A pharmaceutical formulation according to claim 38 wherein the particulates are in dry powder form for aerosolization in a dry powder inhaler.
50. (Original) A pharmaceutical formulation according to claim 38 wherein the particulates are suspended in a propellant for aerosolization in a metered dose inhaler.
51. (Original) A pharmaceutical formulation according to claim 38 wherein the particulates are suspended within a liquid for aerosolization in a nebulizer.
52. (Original) A pharmaceutical formulation according to claim 38 wherein the particulates further comprise a polyvalent cation.
53. (Currently Amended) A pharmaceutical formulation according to claim 38 wherein the particulates are formed by spray drying with a blowing agent.
54. (Currently Amended) A pharmaceutical formulation for pulmonary administration, the pharmaceutical formulation comprising:
particulates comprising an amphotericin B particle in a lipid matrix comprising a phospholipid wherein the amphotericin B particles have a solubility in water of less than 1.0 mg/ml , and are dispersed throughout the phospholipid matrix, and;
wherein the particulates are hollow and/or porous and ~~wherein the particulates~~ have a mass median diameter less than $20 \text{ }\mu\text{m}$, a bulk density of less than about 0.5 g/cm^3 and a mass median aerodynamic diameter less than about $2.6 \text{ }\mu\text{m}$.

PATENT
Serial No. 10/750,934
Docket No. 0101.00

55. (Original) A pharmaceutical formulation according to claim 54 wherein the particulates have a mass median diameter less than $10\ \mu\text{m}$.
56. (Original) A pharmaceutical formulation according to claim 54 wherein the particulates have a mass median diameter less than $5\ \mu\text{m}$.
57. (Cancelled)
58. (Original) A pharmaceutical formulation according to claim 54 wherein the amphotericin B particles are crystalline.
59. (Cancelled)
60. (Currently Amended) A pharmaceutical formulation according to claim 54 wherein the lipid matrix comprises one or more of dipalmitoylphosphatidylcholine, ~~distearylphosphatidylcholine~~ distearoylphosphatidylcholine, diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated phosphatidylinositols.
61. (Cancelled)
62. (Original) A pharmaceutical formulation according to claim 54 wherein the particulates have a bulk density less than $0.3\ \text{g/cm}^3$.
63. (Original) A pharmaceutical formulation according to claim 54 wherein the particulates have a bulk density less than $0.2\ \text{g/cm}^3$.

PATENT
Serial No. 10/750,934
Docket No. 0101.00

64. (Original) A pharmaceutical formulation according to claim 54 wherein the particulates are in dry powder form for aerosolization in a dry powder inhaler.
65. (Original) A pharmaceutical formulation according to claim 54 wherein the particulates are suspended in a propellant for aerosolization in a metered dose inhaler.
66. (Original) A pharmaceutical formulation according to claim 54 wherein the particulates are suspended within a liquid for aerosolization in a nebulizer.
67. (Original) A pharmaceutical formulation according to claim 54 wherein the particulates further comprise a polyvalent cation.
68. (Currently Amended) A pharmaceutical formulation according to claim 54 wherein the particulates are formed by spray drying with a blowing agent.
- 69- 83 (Cancelled).
84. (Withdrawn) A method of making a pharmaceutical formulation for pulmonary administration, the method comprising: suspending amphotericin B particles and a hydrophobic material in a liquid feedstock, wherein at least 90% of the active agent particles have a geometric diameter less than 3 μm ; and spray drying the feedstock suspension to produce particulates comprising amphotericin B at least partially in the hydrophobic material.
85. (Withdrawn) A method according to claim 84 further comprising collecting the particulates, wherein the collected particulates have a mass median diameter less than 20 μm .
86. (Withdrawn) A method according to claim 84 further comprising collecting the particulates, wherein the collected particulates have a mass median diameter less than 10 μm .

PATENT
Serial No. 10/750,934
Docket No. 0101.00

87. (Withdrawn) A method according to claim 84 wherein the hydrophobic material comprises a lipid.
88. (Withdrawn) A method according to claim 84 wherein the hydrophobic material comprises a phospholipid.
89. (Withdrawn) A method according to claim 84 wherein the hydrophobic material comprises a hydrophobic amino acid.
90. (Withdrawn) A method according to claim 84 further comprising adding an emulsifying agent to the feedstock.
91. (Withdrawn) A method according to claim 84 further comprising adding a blowing agent to the feedstock.
92. (Withdrawn) A method according to claim 84 further comprising adding a polyvalent cation to the feedstock.
93. (Withdrawn) A method according to claim 84 wherein the feedstock is spray dried in a manner to produce particulates having a bulk density of less than 0.5 g/cm^3 .
94. (Withdrawn) A pharmaceutical formulation prepared by a method according to claim 84.
95. (Withdrawn) A method of making a pharmaceutical formulation for pulmonary administration, the method comprising: suspending amphotericin B particles in a liquid feedstock, the liquid feedstock having a lipid and a blowing agent dissolved or suspended therein; and spray drying the feedstock suspension to produce hollow and/or porous particulates comprising amphotericin B and the lipid.

PATENT
Serial No. 10/750,934
Docket No. 0101.00

96. (Withdrawn) A method according to claim 95 further comprising collecting the particulates, wherein the collected particulates have a mass median diameter less than 20 μm .
97. (Withdrawn) A method according to claim 95 further comprising collecting the particulates, wherein the collected particulates have a mass median diameter less than 10 μm .
98. (Withdrawn) A method according to claim 95 wherein the lipid comprises a phospholipid.
99. (Withdrawn) A method according to claim 95 further comprising adding an emulsifying agent to the feedstock.
100. (Withdrawn) A method according to claim 95 further comprising adding a polyvalent cation to the feedstock.
101. (Withdrawn) A method according to claim 95 wherein the feedstock is spray dried in a manner to produce particulates having a bulk density of less than 0.5 g/cm³.
102. (Withdrawn) A pharmaceutical formulation prepared by a method according to claim 95.
103. (New) A pharmaceutical formulation according to claim 1 wherein the active agent comprises ciprofloxacin.